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Abstract: BACKGROUND Kaposi's sarcoma (KS), the most common AIDS related cancer, represents a major public concern in resource-limited countries. Single nucleotide polymorphisms within the Interferon lambda 3/4 region (IFNL3/4) determine the expression, function of IFNL4, and influence the clinical course of an increasing number of viral infections. OBJECTIVES To analyze whether IFNL3/4 variants are associated with susceptibility to AIDS-related KS among men who have sex with men (MSM) enrolled in the Swiss HIV Cohort Study (SHCS). METHODS The risk of developing KS according to the carriage of IFNL3/4 SNPs rs8099917 and rs12980275 and their haplotypic combinations was assessed by using cumulative incidence curves and Cox regression models, accounting for relevant co-variables. RESULTS KS was diagnosed in 221 of 2558 MSM Caucasian SHCS participants. Both rs12980275 and rs8099917 were associated with an increased risk of KS (cumulative incidence 15% versus 10%, $P = 0.01$ and 16% versus 10%, $P = 0.009$ respectively). Diplotypes predicted to produce the active P70 form (cumulative incidence 16% versus 10%, $P = 0.01$) but not the less active S70 (cumulative incidence 11% versus 10%, $P = 0.7$) form of IFNL4 were associated with an increased risk of KS, compared to those predicted not to produce IFNL4. The associations remained significant in a multivariate Cox regression model after adjustment for age at infection, combination antiretroviral therapy, median CD4 T-cell count nadir and CD4 slopes (HR = 1.43, 95% confidence interval 1.06-1.93, $P = 0.02$ for IFLN P70 versus no IFNL4). CONCLUSION This study reports for the first time an association between IFNL3/4 polymorphisms and susceptibility to AIDS-related KS.

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**IFNL3/4 polymorphisms are associated with
AIDS-related Kaposi's sarcoma**

IFNL3/4 polymorphism and Kaposi's sarcoma

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Abstract

Background: Kaposi's sarcoma (KS), the most common AIDS related cancer, represents a major public concern in resource-limited countries. Single nucleotide polymorphisms within the Interferon lambda 3/4 region (IFNL3/4) determine the expression, function of IFNL4, and influence the clinical course of an increasing number of viral infections.

Objectives: To analyze whether *IFNL3/4* variants are associated with susceptibility to AIDS-related KS among men who have sex with men (MSM) enrolled in the Swiss HIV Cohort Study (SHCS).

Methods: The risk of developing KS according to the carriage of *IFNL3/4* SNPs *rs8099917* and *rs12980275* and their haplotypic combinations was assessed by using cumulative incidence curves and Cox regression models, accounting for relevant co-variables.

Results: KS was diagnosed in 221 of 2558 MSM Caucasian SHCS participants. Both *rs12980275* and *rs8099917* were associated with an increased risk of KS (cumulative incidence 15% versus 10%, $P=0.01$ and 16% versus 10%, $P=0.009$ respectively). Diplotypes predicted to produce the active P70 form (cumulative incidence 16% versus 10%, $P=0.01$) but not the less active S70 (cumulative incidence 11% versus 10%, $P=0.7$) form of IFNL4 were associated with an increased risk of KS, compared to those predicted not to produce IFNL4.

The associations remained significant in a multivariate Cox regression model after adjustment for age at infection, combination antiretroviral therapy, median CD4⁺ T-cell count nadir and CD4⁺ slopes (HR=1.43, 95% confidence interval 1.06-1.93, $P=0.02$ for IFLN P70 versus no IFNL4).

Conclusion: This study reports for the first time an association between *IFNL3/4* polymorphisms and susceptibility to AIDS-related KS.

Keywords: Kaposi's sarcoma, polymorphism, immunogenetics, IFNL3, AIDS, HIV

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Introduction

Kaposi's sarcoma (KS) was initially described by Moritz Kaposi in 1872 as a rare and relatively indolent angioproliferative neoplasm affecting elderly men from countries surrounding the Mediterranean Sea (classical form of KS) [1]. Another form was described in sub-Saharan Africa in the 1950s, which affects middle aged adults and children (endemic form of KS) [2]. In 1981, a potentially fatal form of KS was described among young homosexual men as a characteristic feature of the AIDS epidemics (epidemic form of KS), a population in which it still represents one of the most common AIDS related cancer [3-8]. An invasive form can also affect patients with non-AIDS immune suppression, in particular solid organ transplant (SOT) recipients (iatrogenic form of KS, reviewed in [2]).

While the four epidemiological forms of KS share the same histological characteristics [9] and are all subsequent to human herpes virus 8 (HHV-8) infection [10, 11], the development of distinct clinical features seems to rely on a combination of host and environmental factors. While HIV- or drug-related immune suppression is inherent to the epidemic and iatrogenic forms (AIDS and SOT), genetic predisposition may be required for the classical (Mediterranean and Jewish ancestry) [12-14] and endemic forms (Sub-Saharan Africa) [15]. Hormonal factors [16-19] have been proposed to explain the male predominance of all forms of Kaposi sarcoma. Environmental conditions relative to potential routes of infection (soil, animal vectors) have been proposed to influence susceptibility to different forms of KS [20-25]. While viral factors may influence clinical presentation, evidence for a definite link between a specific subtype strain and a KS type is still lacking [26-29].

Several investigators have analyzed the role of host genetic factors in susceptibility to KS within a given populations at risk. The most relevant was a polymorphism within the *IL-6* promoter, which was consistently more frequent among KS patients versus controls in two cohorts of AIDS patients [30, 31] and a small cohort of SOT patients [32]. Polymorphisms in other candidate genes (e.g. MHC- or cytokines/chemokines-related genes) were associated with KS in studies of AIDS patients [31, 33-35] and two studies including patients with the classical form of KS [36, 37].

Single nucleotide polymorphisms (SNPs) in the region encoding for interferon lambda 3 (*IFNL3* previously named *IL-28B*) and interferon lambda 4 (*IFNL4*) represent major factors in the ability of individuals to clear HCV [38-41]. They determine different haplotypic combinations (diplotypes) based on their capacity to produce *IFNL4*, i.e. no production versus production as an active P70 or less active S70 form [42-44]. *IFNL3/4* SNPs are increasingly known to influence the susceptibility to or the clinical course of infections due to viruses other than HCV, including herpes viruses such as CMV and EBV [45-47]. Here, we hypothesize that *IFNL3/4* polymorphisms influence the risk to develop KS in AIDS patients.

Material and Methods

Study patients. The Swiss HIV Cohort Study (SHCS) is an ongoing multicenter prospective study of HIV-infected patients enrolled at seven major Swiss hospitals and their local affiliated centers since 1988 [48]. For the present study, Caucasian men who have sex with men (MSM) with available DNA for genotyping and a written informed consent for genetic studies were included. In order to account for the time at risk, only patients with an estimated date of HIV infection were selected [49]. Demographic characteristics including age, duration of HIV

infection, CD4 T-cell count nadir, other opportunistic infections, HIV maximal viral load and HAART use were extracted from the SHCS clinical database. Kaposi sarcoma was defined according to predefined clinical and histological criteria.

SNP genotyping. Genomic DNA isolated either from blood or cell pellets was genotyped for haplotype tagging SNPs *rs8099917* and *rs12980275* using a customized GoldenGate Genotyping Assay on Veracode® platform (Illumina®, San Diego, CA, USA). These SNPs were used as surrogates for *rs368234815* and *rs117648444*, respectively, based on previously published LD values, which were shown to determine the three main diplotypic forms of *IFNL4*. (refs)

Statistical analysis. Statistical analyses were performed using Stata (version 14.2, StataCorp LP, College Station, TX). Hardy-Weinberg equilibrium (HWE) was verified using the program *genhw* implemented in Stata. Haplotypes were inferred using the Phased and grouped according their ability to express the different forms of *IFNL3/4* as described previously [43]. The association of *IFNL3/4* polymorphisms with Kaposi's sarcoma was assessed by 25 year-cumulative incidence curves as well as uni- and multivariable Cox regression models, using the estimated date of HIV infection as a starting point, with censoring at death and/or lost follow-up. Stepwise (i.e. backward) regression ($P < 0.1$) was used to determine which variables were independently associated with the endpoint. The proportional hazard assumption was verified by using the *stphtest* command implemented in Stata. Estimated dates of HIV infection and CD4 slopes in both incident and prevalent cases were obtained by using a joint back calculation model as described previously [50].

Results

The study included 2558 MSM patients among whom 221 developed KS (8.6%, **Supplementary Table 1**, <http://links.lww.com/QAD/B360>). Considering the whole patient, the median age at estimated date of HIV infection was 34 (interquartile range, IQR=13). The median CD4⁺ T cells nadir was 181 cells/mm³ (IQR=174) and the maximal HIV RNA viral load 5.12 log₁₀ copies/ml (IQR=0.85). Most individuals started HAART therapy during follow-up (97%). An active HBV infection was recorded in 10% of patients and HCV serology was positive in 8%.

The minor allele frequencies (MAFs) of IFNL3/4 *rs12980275* and *rs8099917* were 0.30 and 0.20, respectively, and both were at HWE. Carriage of *rs12980275* and *rs8099917* were both associated with an increased risk of KS (CI 15% versus 10%, P=0.01 and CI 16% versus 10%, P=0.009, respectively, **Figure 1**). Diplotypes predicted to produce the active P70 form of IFNL4, but not those predicted to produce the less active S70 form were associated with an increased risk of KS, compared to diplotypes not producing IFNL4 (CI 16% versus 10%, P=0.01 and CI 11% versus 10%, P=0.7, respectively)

The association between IFNL4P70-producing diplotypes and KSA remained significant in a multivariate Cox regression model, accounting for age at infection, HAART, median CD4⁺ T-cell count nadir and CD4⁺ slopes [(hazard ratio 1.43, 95% confidence interval (CI) 1.06-1.93, P=0.02), **Table 1**].

Discussion

Polymorphisms in the region encoding for IFNL3 and 4 have been identified for their major role in the ability of individuals to clear HCV. Increasing evidence suggests that such polymorphisms can also influence the clinical course of infections due to viruses other than HCV [51, 52], in particular those from the Herpesviridae family (CMV [45, 46], EBV [47] and HSV [53]). In this study, we report for the first time an association between *IFNL3/4* polymorphisms and susceptibility to Kaposi's sarcoma among HIV-infected MSM.

An increasing number of *in vitro* studies support the role of IFNL in the immunopathogenesis of viral infections due to viruses other than HCV. A series of cell culture-based models have shown that IFNL3/4 controls the replication of viruses such as human [54] and murine CMV [55], HSV2 [56], HBV [57], dengue virus [58], human metapneumovirus (hMPV) [59], influenza virus [60-62], lymphocytic choriomeningitis virus (LCMV) [63] and Sendai virus [64]. While no studies have analyzed the direct role of IFNL on HHV-8 replication, the involvement of IFNL in its immunopathogenesis is supported indirectly by at least two studies. Those showed that HHV-8 can inhibit IFN transcription by the production of interferon regulatory factor (IRF) homologues as well as block the expression of interferon stimulating genes (ISGs) through JAK-STAT pathway interference [65, 66].

Haplotypic combinations predicted to produce the P70 active, but not the S70 less active form of IFNL4, were associated with an increased risk of KS. This is consistent with the association reported in other viral infections; SNPs encoding or tagging the P70 IFNL4 induce a higher susceptibility to HCV [42, 44], CMV [45, 46], EBV [47] and HSV [53]. This paradoxical effect

of IFNL4 may rely on at least 3 different mechanisms. First, IFNL4 may compete with the other IFNLs through a mechanisms involving the overexpression of its IFNLR1 subunit [67]. Second, IFNL4 may induce a refractory state of the pathway due to persistent ISG expression [43]. Third, individuals expressing the active form of IFNL4 may in return produce lower amount of IFNL3, with subsequent reduced ISG expression [42, 68, 69]. The resulting balance between IFNL3 and IFNL4 expression may be particularly relevant in KS lesions, given the presence of numerous recruited plasmacytoid dendritic cells (pDC), which represent the most important producer of these cytokines [70].

Beyond antiviral properties, IFNLs may also exert anti-tumoral activities including a growth inhibitory effect and apoptosis of tumor cells, as recently described in culture of melanoma [71], lung adenocarcinoma [72, 73], neuroendocrine cancer [74], colorectal carcinoma [75], esophageal carcinoma [76] and hepatocellular carcinoma [77] cells or in mouse models of melanoma [78], colon adenocarcinoma [78] and fibrosarcoma [79]. In humans, the expression of IFNL1 has been negatively correlated with the progression of cervical cancer due to papilloma virus [80], suggesting a potential role of this cytokine in cancer immunity. Altogether, these data suggest that polymorphisms in IFNLs may not only influence the immunity against HHV-8, but also immunity against KS cancer cells.

Like most genetic association studies, our study performed on HIV-infected MSM is constrained by some limitations. Data on HHV-8 sero-prevalence are not available in the SHCS cohort, thereby preventing analyses limited to patients with Kaposi sarcoma but excluding HHV-8 positive individuals who did not develop KS. This limitation may be at least in part compensated by the fact that the prevalence of HHV-8 among MSM is elevated [81, 82] and that the

prevalence of KS and HHV-8 is very well correlated in HIV-infected populations [83-85]. Most likely the currently chosen analytic approach would under- but not overestimated the effect of IFL polymorphisms.

In summary, our data show an association between *IFNL3/4* polymorphism and the development of KS among HIV+ MSM patients. This new finding confirms that IFNLs mediate anti-viral responses against a growing range of viruses.

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Author's contributions.

SB performed sample management, DNA extraction, candidate SNP genotyping, statistical analysis and wrote the manuscript.

AW performed SNP genotyping for the SHCS patients and data management.

PT contributed to statistical analyses.

Members of the SHCS group including, PET, EB, HF, HFG, MH, LK, MO, JF, MC were directly involved in the clinical care of SHCS patients and data acquisition.

PYB designed the SHCS genetic project, obtained funding, supervised genotyping, performed data management and statistical analysis and wrote the manuscript.

All authors critically revised the manuscript.

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Appendix. The members of the Swiss HIV Cohort Study are: Anagnostopoulos A, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Günthard H (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Huber M, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother & Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R, Yerly S.

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Table 1. Independent risk factors associated with KS among MSM.

Variable	Univariate		Multivariate	
	HR (95% CI) ¹	P	HR (95% CI)	P
Age at estimated date of infection	1.01 (1.00-1.03)	0.07	1.05 (1.00-1.11)	0.07
CD4 ⁺ nadir ² (sqrt transformed, continuous)	0.99 (0.99-1.00)	<0.001	1.00 (0.99-1.00)	<0.001
CD4 ⁺ slope ³ (continuous)	0.69 (0.58-0.81)	<0.001	0.84 (0.70-1.02)	0.07
Maximal HIV RNA load (continuous)	1.21 (1.01-1.44)	0.04	1.02 (0.84-1.24)	0.85
HAART (time-dependant covariate)	2.96 (0.74-11.93)	0.13	0.38 (0.26-0.55)	<0.001
HCV co-infection ⁴	0.92 (0.55-1.53)	0.75		
Active HBV infection ⁵	1.32 (0.78-2.24)	0.30		
SNPs				
<i>IFNL3/4 rs12980275</i> (AA versus AG or GG)	1.36 (1.04-1.77)	0.03		
<i>IFNL3/4 rs8099917</i> (TT versus TG or GG)	1.40 (1.07-1.82)	0.01		
Diotypes				
No IFNL4	Reference		Reference	
IFNL4 P70	1.40 (1.05-1.87)	0.02	1.43 (1.06-1.93)	0.02
IFNL4 S70	1.09 (0.74-1.61)	0.67	1.06 (0.69-1.60)	0.80

HR stands for hazard ratio; CI, confidence interval; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HBV, hepatitis B virus. Stepwise (i.e. backward) regression (P<0.2) was used to determine which variables were independently associated with the endpoint.

¹ The proportional hazard assumption was verified for all variables with the exception of CD4⁺ slope. However, the association between IFNL4P70 and KS was similar when CD4⁺ slope was removed from the multivariate model (HR 1.33, 95% CI 1.07–1.65, P=0.01)

² The CD4⁺ nadir square root was used to obtain a normally distributed variable

³ Rate of CD4⁺ depletion in the absence of HAART

⁴ Reflected by HCV serology

⁵ Defined by the presence of HBsAg in the blood

Figure legend

Figure 1. Cumulative incidence of Kaposi's sarcoma according to IFNL4 *rs12980275* (A), IFNL3/4 *rs8099917* (B), IFNL4P70 (C) in MSM participants of the SHCS. The estimated date of HIV infection was used as a starting point with censoring at death or lost follow-up. (n) indicates the number of patients with KS in each group of patients. P values were calculated by log-rank test, dominant mode.



